

## PATENT ABSTRACTS OF JAPAN

(11)Publication number : 05-249097

(43)Date of publication of application : 28.09.1993

(51)Int.Cl.

G01N 33/15  
// A61K 9/20

(21)Application number : 04-083230

(71)Applicant : YAMANOUCHI PHARMACEUT CO  
LTD

(22)Date of filing : 04.03.1992

(72)Inventor : MIZUMOTO TAKAO  
SAKO KAZUHIRO  
FUKUI MUNEO  
OMURA TADAYOSHI

## (54) ELUTION TEST METHOD FOR ESTIMATING IN VIVO ELUTION OF TABLET

## (57)Abstract:

PURPOSE: To predict the concentration of a gradually releasable tablet in blood plasma inside a living body without being affected by the release control mechanism of the gradually releasable tablet by a method wherein the tablet is eluted for a prescribed time, it is taken out once, it is treated with oils and fats and it is stirred and eluted together with a bead or it is put into a sinker, stirred and eluted.

CONSTITUTION: A tablet is eluted for a prescribed time at 15 to 50 revolutions per minute by using a paddle method. The tablet is taken out once and treated with oils and fats; it is stirred and eluted at 15 to 50 revolutions per minute together with beads, or it is put into a sinker, stirred and eluted at 100 to 200 revolutions per minute. The elution amount of a medicine at intervals of a prescribed time is measured, and the elution inside a living body is presumed. A test solution is not limited as long as it is a liquid which has been adjusted to the pH value of a part presuming the behavior of the elution inside the living body of a tablet under test. The tablet which is applied is gradually releasable tablet. It is not limited especially as long as it is a tablet required to presume the behavior of a release inside the living body. It may be provided with any release control mechanism. Consequently, a hydrogel preparation or a matrix preparation may be used.

## LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

Copyright (C); 1998,2000 Japan Patent Office

## Computer-generated translation of JP-05-249097

[Claim(s)]

*Pharmacopoeia*

[Claim 1] Predetermined time elution of the tablet is carried out by the rotational frequency 15 - 50rpm by the Japanese station elution test method second method (the paddle method) (paddle elution process). After once taking out a tablet and processing with fats and oils by request, (bead elution process) [ whether churning elution is carried out by the rotational frequency 15 - 50rpm with a bead, and ] Or the method of presuming elution in the living body by putting into a sinker, carrying out churning elution by the rotational frequency 100 - 200rpm (stationery elution process), and measuring the elution volume of the medicine for every predetermined time [a claim 2] Technique according to claim 1 fats and oils are a half-solid or a solid in ordinary temperature [a claim 3] Technique according to claim 2 fats and oils are hardened oil [a claim 4] Technique according to claim 1 characterized by performing a bead elution process after performing a paddle elution process, once taking out a tablet and processing with fats and oils [a claim 5] Technique according to claim 1 characterized by performing a stationery elution process after performing a paddle elution process, once taking out a tablet and processing with fats and oils

[Detailed Description of the Invention]

[0001]

[Field of the Invention] this invention -- a tablet -- it faces designing or evaluating a sustained release drug especially, and the exudation behavior of a medicine in the living body can be predicted exactly in vitro It is related with the elution test technique.

[0002]

[Description of the Prior Art] It is known that the drug release in an alimentary canal will be influenced by various physiological factors. When drug release is mainly influenced by a fluidity or agitating speeds, such as pH, among these physiological factors, also in the present paddle method, it is thought that exudation behavior in the living body is reproducible.

[0003] However, when drug release was influenced by factors, such as a factor made to insolubilize a tablet by the mechanical force based on the enterokinesis which is factors other than these, the meal component, and the living body origin component, it was difficult to reproduce exudation behavior in the living body by the present paddle method. the technique of presuming the exudation behavior of a medicine in the living body [ conventional ] \*\*\*\*\* -- for example -- Int.J.Pharm.60 (1990), and 151-156 \*\*\*\*\* -- although the method of performing an elution test among a phosphoric-acid buffer solution using the sustained release drug of ferro \*\*\*\*\* was learned, it was not satisfactory in order for exudation behavior in the living body to have been reproducible

[0004]

[Problem(s) to be Solved by the Invention] this invention person etc. can predict exudation behavior in the living body, when designing or evaluating a sustained release

drug especially, a tablet and. in vitro this invention was completed as a result of inquiring zealously about the elution test technique.

[0005]

[Means for Solving the Problem] That is, the elution behavior of the tablet characterized by this invention consisting of each following process in the living body is presumed. in vitro It is the elution test technique.

- 1) The process which carries out 15-50rpm predetermined time elution of the tablet by the paddle method (paddle elution process)
- 2) How to presume elution in the living body by putting into whether churning elution is carried out by the rotational frequency 15 - 50rpm with \*\* bead, and \*\* sinker (henceforth a bead elution process or the bead method), carrying out churning elution by the rotational frequency 100 - 200rpm (henceforth a stationery elution process or the stationery method), and measuring the elution volume of the medicine for every predetermined time once taking out a tablet and processing with fats and oils by request.

[0006] The elution test technique of this invention is explained still in detail below.

(Paddle elution process) namely, the equipment used at a paddle elution process in this invention -- for example, the Pharmacopoea of Japan Commercial-test method It is the equipment which consists of an impeller used by the elution test 2nd method, and a rotation axis. You put an examination tablet into this equipment, and make it preferably eluted by the rotational frequency 15 of an impeller, - 50rpm. A subject tablet is dipped into a container as it is, or it may put into a sinker and it may make it eluted.

[0007] As a testing liquid in this case, it is the Pharmacopoea of Japan. If it is the liquid adjusted to pH in the site which presumes the elution behavior of a subject tablet besides the 1st liquid specified by the commercial-test method:decay examining method, or the 2nd liquid in the living body, there is especially no limit. Furthermore, although the elution time in this case changes with subject tablets, it is about 1 hour more preferably [ it is desirable and ] than less than 2 hours.

[0008] Next, although the tablet applied to this elution test method is a sustained release drug, as long as estimation of exudation behavior in the living body is a required tablet, there is especially no limit and it may have which exudation controlling mechanism. Therefore, as the sustained-release tablet, a hydro gel tablet, a matrix tablet, etc. may be used. Moreover, as an excipient used in order to control elution, there is especially no limit, for example, it can combine one sort or two sorts or more for a water soluble polymer, a water-insoluble nature macromolecule, an enteric nature macromolecule, etc., and can use them for a chief remedy as combination or an elution control layer. As a chief remedy in this case, various medicines, such as hydrochloric-acid \*\*\*\*\* besides the acetaminophen used by this example and hydrochloric-acid \*\*\*\*\*\_\*\*, are adopted. Moreover, there is no limit also in the excipient used in order to \*\* to a tablet, and a lubricant, a binder, an extending agent, etc. are suitably used for it.

[0009] As a water soluble polymer, hydroxypropylcellulose, the hydroxypropyl methylcellulose, a methyl cellulose, a polyethylene glycol, etc. are mentioned, for example. As a water-insoluble nature macromolecule, ethyl-cellulose, cellulose acetate, \*\*\*\*\* RS (copolymer of 1:2:0.1 tradename and loam - and made in [ - Haas ],

and of component:ethyl-acrylate-methyl-methacrylate-trimethylammonium ethyl methacrylate chloride), and \*\*\*\*\* RS100L (copolymer of 1:2:0.2 tradename and loam - and made in - Haas, and of component:ethyl-acrylate-methyl-methacrylate-trimethylammonium ethyl methacrylate chloride) etc. is mentioned, for example.

[0010] As an enteric nature macromolecule, CMEC (a tradename, Freund Industrial make : carboxy methyl ethyl cellulose), hydroxypropyl-methylcellulose \*\*\*\*\*\_\*\*, \*\*\*\*\* S (tradename and loam - and made in - Haas, 2:1 copolymers of a component:methacrylic-acid methyl-methacrylic acid), \*\*\*\*\* L (tradename and loam - and made in - Haas, 1:1 copolymers of a component:methacrylic-acid methyl-methacrylic acid), etc. are mentioned, for example.

[0011] Next, fats-and-oils processing of this invention is explained. That is, the tablet eluted at the paddle elution process of this invention is processed by request with fats and oils. As fats and oils in this case, it is fats and oils half-solid with ordinary temperature, or solid, and, specifically, higher alcohol, such as animal fat and oils, such as hardened oil of hardening rapeseed oil (the Freund Industrial make, \*\*\*\*\*-wax 103), hydrogenated castor oil (the product made from \*\*\*\* Fine chemicals, K-3 wax), and hardening soybean oil, and beef tallow, \*\*\*\*, and a stearyl alcohol, cetyl alcohol, etc. is mentioned. These fats and oils can be suitably changed by the dosage forms of a subject tablet.

[0012] Moreover, once, since fats and oils are a half-solid or a solid in ordinary temperature, after warming and fusing, they put in and process a tablet in this at 40 degrees C or 80 degrees C. Although the time for processing is changed also according to the following elution process, it is 1 or about 10 minutes preferably less than several 10 minutes.

[0013] Next, you put into a <sup>basket</sup> sinker the tablet which the tablet processed with fats and oils is made eluted by rotational frequency 15-50rpm with the equipment which consists of an impeller and a rotation axis with \*\* bead, or was processed with \*\* fats and oils, and make it eluted by the rotational frequency 100 - 200rpm in the exam technique with the equipment which serves as an impeller from a rotation axis.

[0014] It examines, giving the mechanical force to a tablet by the physical impact by the bead which is introduced in order to face these elution processes presuming the elution behavior of a tablet in the living body and to have influence of the mechanical force, and was introduced in equipment, or the stream produced by rotation of a rotary wing.

\*\* As shown in drawing 1 , a bead elution process this gentleman method puts the tablet processed with fats and oils into the equipment which consists of an impeller and a rotation axis with a bead, and is performed by preparing the rotational frequency of a rotary wing to 15 - 50rpm.

[0015] In this case, since the mechanical force which the rotational frequency of the rotary wing which can be set is contained in equipment of a bead with the tablet, and a tablet receives is comparatively large, a rotational frequency may be late. It is about 25 rpm more preferably [ as a rotational frequency in this case, it is desirable, and ] than 15-50rpm. Moreover, especially as a bead, if it is the quality of the material and the size which do not affect rotation of a rotary wing, there is especially no limit, for example,

they are a glass bead, a Teflon bead, a polystyrene bead, etc. Moreover, 50-400g of the amount is about [ 100g ] preferably.

[0016] \*\* A stationery elution process this gentleman method puts into a sinker the tablet processed with fats and oils as shown in drawing 2 , and is performed by the Pharmacopoea of Japan elution test method second method by adjusting the rotational frequency of a rotary wing to 100 - 200rpm. In this elution process, since the tablet is contained in the sinker, it depends for the mechanical force in which a tablet receives on the stream produced by rotation of a rotary wing. Therefore, compared with the rotational frequency in a bead elution process, a quick rotational frequency is desirable, for example, it is 100-200rpm. Moreover, the position of the sinker which put in the tablet is preferably fixed to a wall surface that what is necessary is just the position which receives the mechanical force by the stream.

[0017]

[Effect of the Invention] As long as the exam technique is followed, it is the elution behavior of a tablet in the living body. in vitro It sets and can be reflected exactly. Therefore, the elution test technique of this invention and in vitro It can set, the concentration in plasma in the living body can be predicted, and the tablet design based on it can be performed efficiently. Moreover, the test methods of this invention are a tablet and an epoch-making test method which does not receive influence in the exudation controlling mechanism of a sustained-release tablet especially.

[0018]

[Example] And the test method of this invention is explained to it still in detail. [ below ] [ an example ] this invention is not restricted to these test methods at all.

[0019] the weight ratio 1:1 came out of example of manufacture 1 acetaminophen (AAP), and the hydroxypropyl methylcellulose comparatively, it mixed, and the tablet (GM) with a weight of 200mg was obtained by the direct compressing method

[0020] the weight ratio 2:1 came out of example of manufacture 2 acetaminophen, and the ethyl cellulose comparatively, it mixed, and the tablet (EM) with a weight of 150mg was obtained by the direct compressing method

[0021] Example of manufacture 3 acetaminophen and \*\*\*\*\* RS30D were kneaded at a rate of the weight ratio 2:1 of a solid content, and the tablet (RM) with a weight of 150mg was obtained by the direct compressing method after xeransis.

[0022] Internal use of the sustained-release tablet (100mg of chief-remedy contents) obtained in the example 1 of example of examination 1 manufacture, the example 2 of manufacture, or the example 3 of manufacture was carried out to six male beagles with 20ml of water, it collected blood with time, and the concentration in plasma was measured.

[0023] The example 2 (calculation of the amount in the living body of drug release) of an examination

The concentration data in plasma of the sustained-release tablet which carries out internal use of the aqueous solution (100mg of chief-remedy contents) of an acetaminophen by the same technique as the example 1 of an examination, and makes a weight function the

obtained concentration data in plasma, and was obtained in the example 1 of an examination were made into the output function, and the amount of drug release of a sustained-release tablet in the living body was computed by the deconvolution method.

[0024] The example 3 (forecast of the concentration in plasma) of an examination

The concentration in plasma when making the elution test data which carry out internal use of the aqueous solution (100mg of chief-remedy contents) of an acetaminophen by the same technique as the example 1 of an examination, and make a weight function the obtained concentration data in plasma, and were obtained in each example into an input function, and carrying out internal use of each sustained-release tablet by the convolution method was computed.

[0025] The sustained-release tablet obtained in the example 1 of manufacture, the example 2 of manufacture, or the example 3 of manufacture was examined by rotational-speed 25rpm by the Japanese station elution test method second method, using the 500ml of the Japanese station decay examining method 2nd liquid as example of comparison 1 test solution. The result was shown in drawing 3 . Consequently, it accepted that the almost same elution behavior is shown by GM, EM, and RM, and it accepted that there are exudation behavior of a medicine in the living body and a big difference.

[0026] The sustained-release tablet (GM) obtained in the example 1 of manufacture was examined by rotational-speed 25rpm by the Japanese station elution test method second method, using the 500ml of the Japanese station decay examining method 2nd liquid as example 1 test solution. It is \*\*\*\*\* about an examination at rotational-speed 25rpm by the bead method using glass-bead ( $\phi 4\text{mm}$ ) 100g succeedingly after flooding with the hardening rapeseed oil (\*\*\*\*\* wax 103) which took out the sustained-release tablet from the test solution 1 hour after, and was warmed at 80 degrees C for 10 minutes. The result was shown in drawing 4 . This test result is reflecting elution behavior in the living body exactly almost in accordance with the amount of drug release of the sustained-release tablet of the example 1 of manufacture computed by the example 2 of an examination in the living body. Furthermore, it is mostly in agreement with the concentration in plasma of the survey measured in the example 1 of an examination, and the concentration in plasma computed by the example 3 of an examination as shown in drawing 5 is it \*\*\*\*\* that a forecast of the concentration in plasma is easily possible by this invention from this result.

[0027] The sustained-release tablet (EM) obtained in the example 2 of example 2 manufacture was examined by the same operation as an example 1. The result was shown in drawing 4 . This test result is reflecting elution behavior in the living body exactly almost in accordance with the amount of drug release of the sustained-release tablet of the example 2 of manufacture computed by the example 2 of an examination in the living body. Furthermore, almost in accordance with the concentration in plasma of the survey measured in the example 2 of an examination, the forecast of the concentration in plasma of the concentration in plasma computed by the example 3 of an examination as shown in drawing 5 was easily attained from this result by this invention.

[0028] The sustained-release tablet (RM) obtained in the example 3 of example 3 manufacture was examined by the same operation as an example 1. Furthermore, almost in accordance with the concentration in plasma of the survey measured in the example 1

of an examination, the forecast of the concentration in plasma of the concentration in plasma computed by the example 3 of an examination as shown in drawing 6 was easily attained from this result by this invention.

[0029] The sustained-release tablet (GM) obtained in the example 1 of manufacture was examined by rotational-speed 25rpm by the Japanese station elution test method second method, using the 500ml of the Japanese station decay examining method 2nd liquid as example 4 test solution. The sustained-release tablet was taken out from the test solution 1 hour after, after flooding with the hardening rapeseed oil (\*\*\*\*\* wax 103) warmed at 80 degrees C for 1 minute, the sustained-release tablet was put into the sinker fixed to the vessel-wall side, and the elution test was succeedingly performed by rotational-speed 200rpm by the stationery method. The result was shown in drawing 7 . This test result found this melting reflecting elution behavior in the living body exactly like the bead method (example 1) almost in accordance with the amount of drug release of the sustained-release tablet of the example 1 of manufacture computed by the example 2 of an examination in the living body.

[0030] The sustained-release tablet (EM) obtained in the example 2 of example 5 manufacture was examined by the same operation as an example 4. The result was shown in drawing 7 . This test result found this melting reflecting elution behavior in the living body exactly like the bead method (example 2) almost in accordance with the amount of drug release of the sustained-release tablet of the example 2 of manufacture computed by the example 2 of an examination in the living body.

[0031] The sustained-release tablet (RM) obtained in the example 3 of example 6 manufacture was examined by the same operation as an example 4. As a result, it was shown in view 7 . This test result found this melting reflecting elution behavior in the living body exactly like the bead method (example 3) almost in accordance with the amount of drug release of the sustained-release tablet of the example 3 of manufacture computed by the example 2 of an examination in the living body.



**\* NOTICES \***

**Japan Patent Office is not responsible for any damages caused by the use of this translation.**

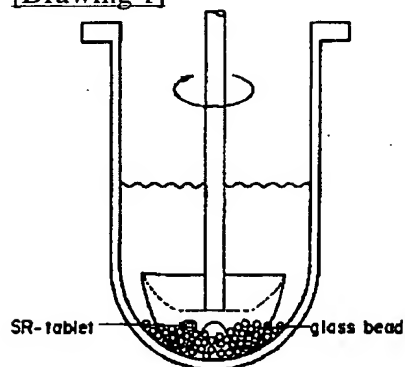
1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. \*\*\*\* shows the word which can not be translated.
3. In the drawings, any words are not translated.

---

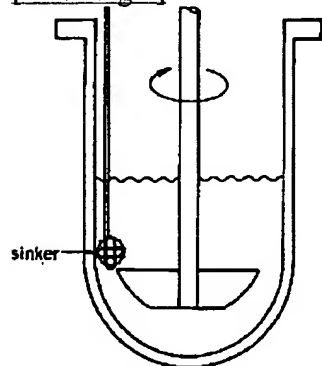
**DRAWINGS**

---

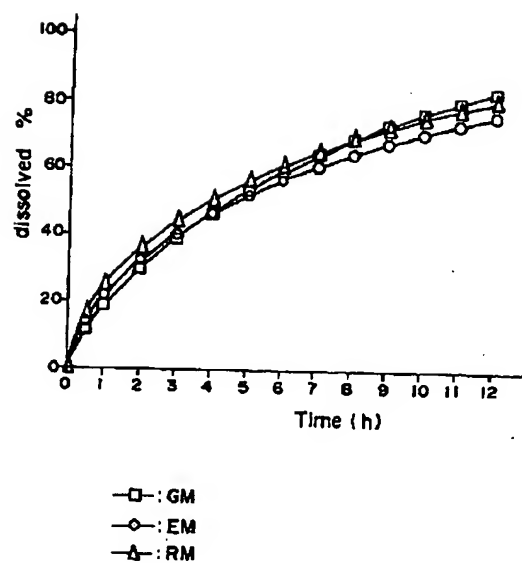
[Drawing 1]



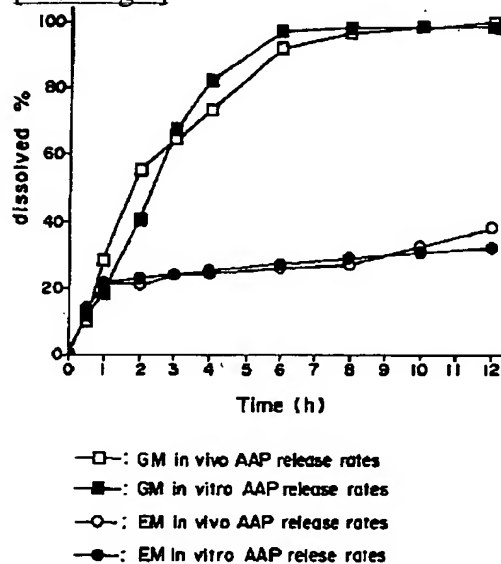
[Drawing 2]



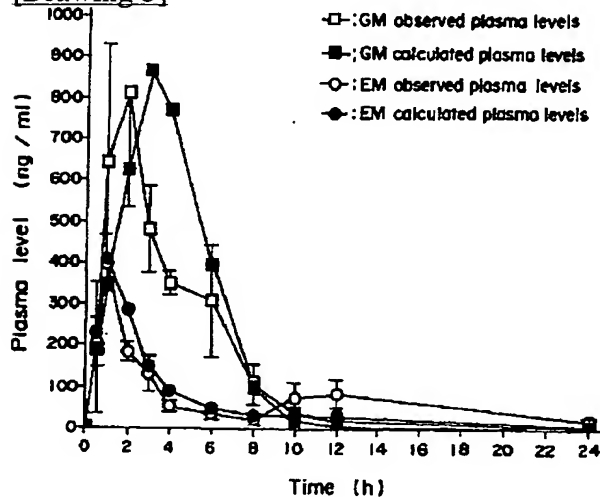
[Drawing 3]



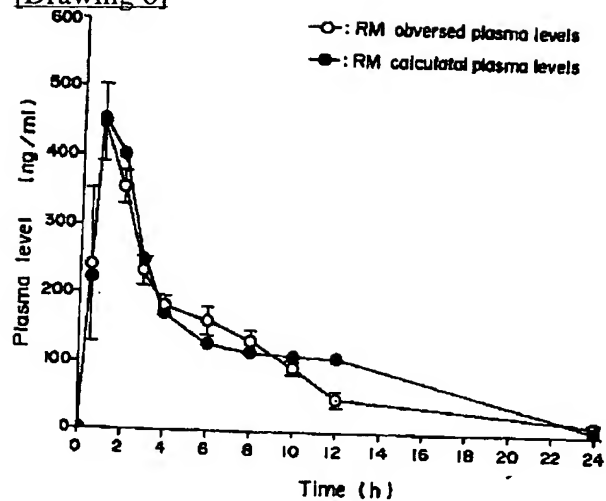
[Drawing 4]



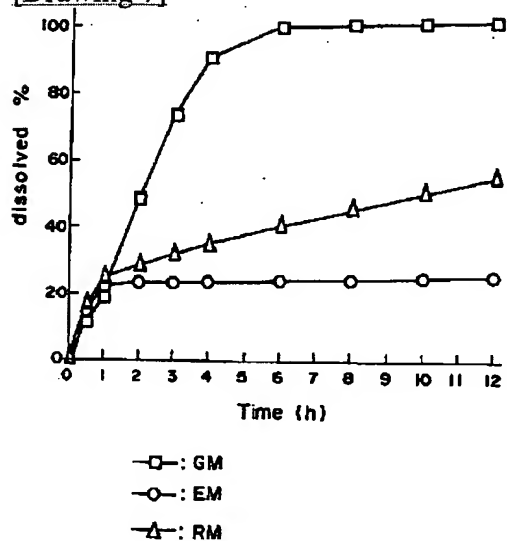
[Drawing 5]



[Drawing 6]



[Drawing 7]



[Translation done.]